

# Exhibit D

# Clinical Review

Interventional Radiology Series

## Using inferior vena cava filters to prevent pulmonary embolism

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### ABSTRACT

**OBJECTIVE** To review the evidence for using inferior vena cava (IVC) filters to prevent pulmonary embolism (PE) in high-risk patients.

**QUALITY OF EVIDENCE** Ovid MEDLINE was searched from 1966 to 2006 for all English-language papers on IVC filters. Evidence was graded according to the 3-level classification system. Most evidence found was level II.

**MAIN MESSAGE** Inferior vena cava filters are used to prevent PE in patients with contraindications to, complications of, or failure of anticoagulation therapy and patients with extensive free-floating thrombi or residual thrombi following massive PE. Current evidence indicates that IVC filters are largely effective; breakthrough PE occurs in only 0% to 6.2% of cases. Contraindications to implantation of IVC filters include lack of venous access, caval occlusion, uncorrectable coagulopathy, and sepsis. Complications include misplacement or embolization of the filter, vascular injury or thrombosis, pneumothorax, and air emboli. Recurrent PE, IVC thrombosis, filter migration, filter fracture, or penetration of the caval wall sometimes occur with long-term use.

**CONCLUSION** When used appropriately, IVC filters are a safe and effective method of preventing PE. Using retrievable filters might reduce long-term complications.

### RÉSUMÉ

**OBJECTIF** Réviser les données concernant l'utilisation des filtres de la veine cave inférieure (VCI) pour prévenir les embolies pulmonaires (EP) chez les patients à risque élevé.

**QUALITÉ DES PREUVES** On a recherché dans Ovid MEDLINE entre 1966 et 2006 tous les articles de langue anglaise sur le filtre de la VCI. Le système à trois niveaux a été utilisé pour classer les preuves. La plupart des données trouvées étaient de niveau II.

**PRINCIPAL MESSAGE** Le filtre de la veine cave inférieure est utilisé pour prévenir les EP chez les patients qui présentent des contre-indications, des complications ou un échec de l'anticoagulothérapie et chez ceux qui ont des thrombi flottants volumineux ou des thrombi résiduels après une EP massive. Les données actuelles indiquent que les filtres de la VCI sont fort efficaces; des EP les franchissent dans seulement 0,0-2,5% des cas. Les contre-indications à leur implantation sont l'absence d'accès veineux, l'occlusion de la veine cave, une coagulopathie non corrigeable ou une septicémie. Les complications incluent: insertion au mauvais endroit ou embolisation du filtre, lésion ou thrombose vasculaire, pneumothorax et embolie gazeuse. À long terme, il peut se produire des EP récurrentes, des thromboses de la VCI, une migration ou une fracture du filtre, ou une pénétration de la paroi de la veine cave.

**CONCLUSION** Le filtre de la VCI, utilisé judicieusement, est une méthode sécuritaire et efficace pour prévenir les embolies pulmonaires. L'utilisation de filtres récupérables pourrait réduire les complications à long terme.

This article has been peer reviewed.

Cet article a fait l'objet d'une révision par des pairs.

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STUDY	TYPE OF STUDY	TYPE OF FILTER	NO. AND TYPE OF PATIENTS	FOLLOW-UP TIME	FINDINGS	RETRIEVAL TIMES	SUCCESSFUL RETRIEVALS	COMPLICATIONS
Hoff et al, <sup>20</sup> 2004	Uncontrolled prospective case series	Günther Tulip retrievable filter	35 patients: indications were blunt trauma with no known thromboembolic disease but contraindication to anticoagulation therapy and mechanical prophylaxis	Range 6–14 d	No PE during hospital stay; 3 DVTs (8.6%) while filter in place	Mean 10.2 d (range 6–14)	18 of 22 attempts were successful (82%)	4 filter thrombi resulting in failed retrieval attempt (11.4%)
Terhaar et al, <sup>21</sup> 2004	Uncontrolled retrospective review with prospective follow-up callback, case series	Günther Tulip retrievable filter	53 patients: indications were planned major surgery with recurrent PE or high PE risk, extensive iliofemoral thrombus, DVT with anticoagulant complications, breakthrough PE despite anticoagulation therapy, and contraindication to anticoagulation therapy	13 mo (for permanent filter patients)	1 case of PE (1.9%)	Median 34 d (range 7–126)	16 of 19 attempts were successful (84%)	1 postretrieval pneumothorax (6.25%); 1 PE 12 h postinsertion (1.9%); 2 right internal jugular vein thromboses (3.8%); 1 transient Horner syndrome postretrieval (6.25%); 3 failed retrieval attempts (2 due to filter thrombi [3.8%], 1 due to adherence to IVC wall [1.9%]); 6 patients died (unrelated to filter placement or retrieval) (11.3%)
Millward et al, <sup>22</sup> 2001	Retrospective (and prospective) multicentre review, case series	Günther Tulip retrievable filter	90 patients: indications were PE or DVT with contraindication to anticoagulation therapy or prophylaxis after massive PE or free-floating thrombus or prophylaxis after trauma or before major surgery	Retrieved: mean 103 d (range 5–420); nonretrieved: mean 85 d (range 7–420)	97.6% technical success (2 wrongly inserted filters), no PE in retrieval or nonretrieval groups	Mean 9 d (range 2–25)	52 of 53 attempts were successful (98%); 1 failure due to initial filter misplacement	Retrieval group: 3 deaths unrelated to filter; 1 misplaced in iliac vein (1.1%), 1 recurrent DVT 230 d postretrieval. Nonretrieval group: 7 deaths unrelated to filter, 10 large filter thrombi precluding planned retrieval (11.1%), 2 IVC occlusions (2.2%)

DVT—deep vein thrombosis, IVC—inferior vena cava, PE—pulmonary embolism, VTE—venous thromboemboli.

pneumatic compression stockings and aggressive mobilization after surgery.

### Referral for placement

Placement of IVC filters is available in all major centres in Canada and in most centres with practising interventional radiologists. Placement and removal of these filters is generally done in hospital for many reasons: the procedure requires technical expertise coupled with adequate fluoroscopic equipment, the complexity of scheduling filter placement with appropriate anticoagulation therapy is more easily managed in hospital, and interventional radiologists generally practise only in hospitals. Ideally, patients should be admitted to hospital if conventional therapy does not work, whether due to noncompliance or otherwise. Physicians providing in-hospital care can then refer their patients to interventional radiology if they feel filter placement is indicated. The ultimate decision for IVC filter placement and removal is a collaborative one between referring physician and radiologist. The procedure could be done on an outpatient basis, but this is not the current norm.

### Future directions

In recent years, use of IVC filters has surged; 1 report showed a greater than 12-fold increase in use from 1979 to 1999.<sup>5</sup> This trend is likely to continue owing to better and safer filters. More importantly, these devices are now being used for other indications, including prophylaxis despite absence of VTE, and in conjunction with anticoagulation therapy to reduce the likelihood of PE occurring in high-risk patients.<sup>5</sup> The quality of evidence is not yet ideal, however. Apart from 1 randomized trial in 2005, most data on these devices are drawn from nonrandomized case series. While these studies show that IVC filters are an acceptable method of preventing PE when anticoagulation therapy is no longer viable, little evidence suggests that IVC filters are prophylactically superior to anticoagulation therapy or that a combination of IVC filters and anticoagulation therapy is better than therapy alone. In fact, no studies to date compare the outcome of IVC filters with medical management. Randomized controlled trials are needed to determine

whether there are substantial differences among the many filters currently used.

Finally, more studies are required to create guidelines for when filters can be removed safely to minimize recurrence of PE and still maximize successful and safe retrieval of the filter.

## Conclusion

Inferior vena cava filters are effective at preventing PE in patients with proven DVT for whom medical anticoagulation is contraindicated or has failed. These filters are also used for patients at high risk of PE even if they do not have DVT. Studies to date show that only a very few cases of PE occur in patients with these filters. ✱

## Competing interests

None declared

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## EDITOR'S KEY POINTS

- Anticoagulation is the first-line therapy for treatment and prevention of pulmonary embolism (PE). In some patients with proven deep-vein thrombosis or at high risk of PE, however, medical anticoagulation is contraindicated or has failed. In these patients, inferior vena cava filters can be used to prevent PE.
- Current evidence indicates that these filters are usually effective in preventing breakthrough PE. Filters can be removed when a patient has an acceptably low risk of PE.
- Short-term complications are usually minor and include access-site hematomas and thrombosis. Complications, such as sepsis or thrombosis, can occur with long-term use.

## POINTS DE REPÈRE DU RÉDACTEUR

- L'anticoagulation est l'intervention de choix pour traiter et prévenir l'embolie pulmonaire (EP). Toutefois, chez certains patients présentant une thrombose veineuse profonde bien démontrée ou un fort risque d'EP, l'anticoagulation peut être contre-indiquée ou ne pas réussir. Chez ces derniers, le filtre de la veine cave inférieure peut être utilisé pour prévenir les EP.
- D'après les données actuelles, ce filtre est généralement efficace pour prévenir le passage de nouvelles EP. Il peut être retiré lorsque le risque d'EP est suffisamment bas.
- Les complications à court terme sont généralement peu sévères, telles des hématomes ou thromboses au site d'entrée. À long terme, des complications de septicémie ou de thrombose peuvent survenir.